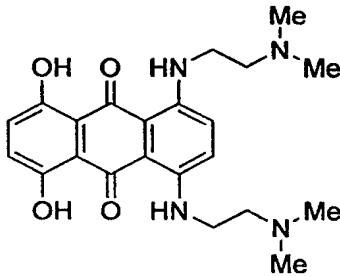
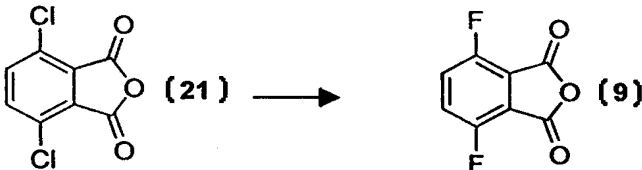




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁷ : C07C 221/00, 225/36, 291/04</p>	<p>A1</p>	<p>(11) International Publication Number: WO 00/05194</p> <p>(43) International Publication Date: 3 February 2000 (03.02.00)</p>		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> <p>(21) International Application Number: PCT/GB99/02337</p> <p>(22) International Filing Date: 20 July 1999 (20.07.99)</p> <p>(30) Priority Data: 9815910.6 21 July 1998 (21.07.98) GB</p> <p>(71) Applicant (for all designated States except US): BTG INTERNATIONAL LIMITED [GB/GB]; 10 Fleet Place, Limeburner Lane, London EC4M 7SB (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): DENNY, William, Alexander [NZ/NZ]; 165 Gossamer Drive, Pakuranga, Auckland (NZ). LEE, Ho, Huat [NZ/NZ]; 57a Disraeli Street, Mount Eden, Auckland (NZ).</p> <p>(74) Agent: ENGLAND, Christopher, David; BTG International Limited, Patents Dept., 10 Fleet Place, Limeburner Lane, London EC4M 7SB (GB).</p> </td> <td style="width: 50%; vertical-align: top; padding: 5px;"> <p>(81) Designated States: CA, JP, MX, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> </td> </tr> </table>			<p>(21) International Application Number: PCT/GB99/02337</p> <p>(22) International Filing Date: 20 July 1999 (20.07.99)</p> <p>(30) Priority Data: 9815910.6 21 July 1998 (21.07.98) GB</p> <p>(71) Applicant (for all designated States except US): BTG INTERNATIONAL LIMITED [GB/GB]; 10 Fleet Place, Limeburner Lane, London EC4M 7SB (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): DENNY, William, Alexander [NZ/NZ]; 165 Gossamer Drive, Pakuranga, Auckland (NZ). LEE, Ho, Huat [NZ/NZ]; 57a Disraeli Street, Mount Eden, Auckland (NZ).</p> <p>(74) Agent: ENGLAND, Christopher, David; BTG International Limited, Patents Dept., 10 Fleet Place, Limeburner Lane, London EC4M 7SB (GB).</p>	<p>(81) Designated States: CA, JP, MX, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(21) International Application Number: PCT/GB99/02337</p> <p>(22) International Filing Date: 20 July 1999 (20.07.99)</p> <p>(30) Priority Data: 9815910.6 21 July 1998 (21.07.98) GB</p> <p>(71) Applicant (for all designated States except US): BTG INTERNATIONAL LIMITED [GB/GB]; 10 Fleet Place, Limeburner Lane, London EC4M 7SB (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): DENNY, William, Alexander [NZ/NZ]; 165 Gossamer Drive, Pakuranga, Auckland (NZ). LEE, Ho, Huat [NZ/NZ]; 57a Disraeli Street, Mount Eden, Auckland (NZ).</p> <p>(74) Agent: ENGLAND, Christopher, David; BTG International Limited, Patents Dept., 10 Fleet Place, Limeburner Lane, London EC4M 7SB (GB).</p>	<p>(81) Designated States: CA, JP, MX, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>			
<p>(54) Title: PROCESS FOR THE PREPARATION OF 1,4-BIS[[2- (DIMETHYLAMINO) ETHYL] AMINO] -5,8- DIHYDROXYANTHRACENE- 9,10-DIONE</p> <p>(57) Abstract</p> <p>A process for the preparation of the compound AQ4 of formula (3) or a salt or N-oxide thereof, includes the step (21-9).</p> <div style="text-align: center; margin-top: 20px;">  <p style="margin-left: 750px;">(3)</p> </div> <div style="text-align: center; margin-top: 30px;">  </div>				

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

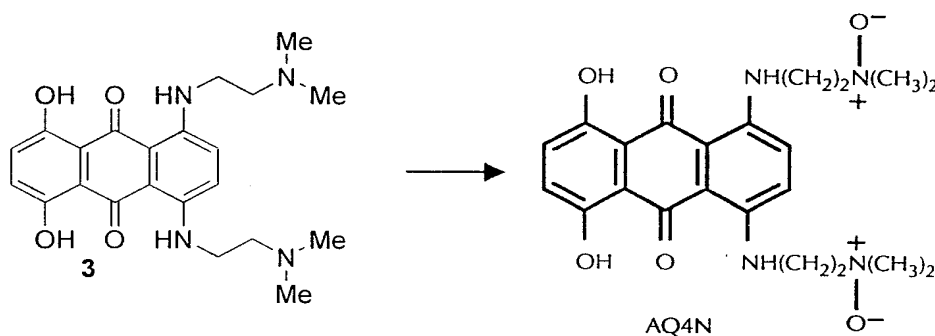
AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PROCESS FOR THE PREPARATION OF 1,4-BIS[[2- (DIMETHYLAMINO) ETHYL] AMINO] -5,8- DIHYDROXYANTHRAQUINONE- 9,10-DIONE

The invention relates to a process for the preparation of AQ4 and derivatives thereof including AQ4N, a bis-bioreductive agent with of value in the treatment of cancer.

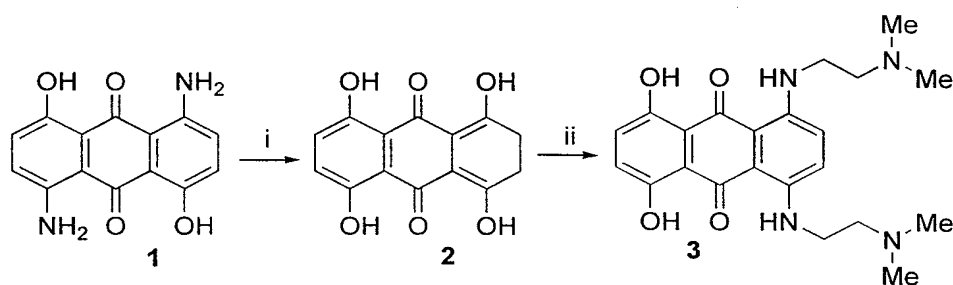
5

AQ4N is an anthraquinone, and would normally be synthesised by oxidation of AQ4 (3):



AQ4N is in fact a prodrug and the reverse reaction occurs *in vivo*, reductive metabolism in hypoxic cells giving the active agent, AQ4, in its protonated form. The prodrug is non-toxic, making its synthesis in large quantities desirable.

AQ4 has been prepared previously by the method of Scheme 1 (*J. Chem. Soc.* 1937, 254; *J. Med. Chem.* 1979, 22; *Synth. Comm.* 1995, 25, 1893).



Scheme 1 i: NaOH/Na₂S₂O₄/H₂O/70-100 °C.
ii: Me₂N(CH₂)₂NH₂/EtOH/50-60 °C/21 h, then air oxidation.

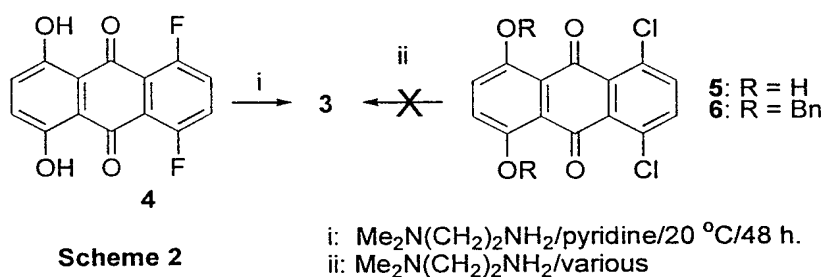
15

Alternatively, 1,8-diamino-4,5-dihydroxyanthraquinone (US \$14/1g: Aldrich Chemical Co., Gillingham, England) can be substituted for **1** in Scheme 1. We have also prepared **3** by the route as shown in Scheme 1, and found that the leuco compound **2** was formed in low purity, but was too unstable to be purified. Subsequent direct use of

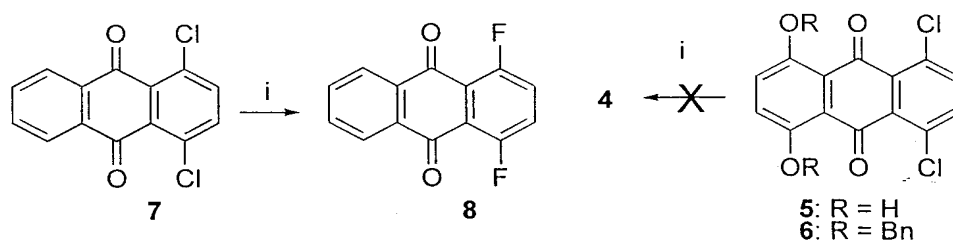
this led to impure 3, which required extensive column chromatography to obtain material pure enough to crystallise. The overall yield of 3 from 1 was 33% (of 90–97% purity) following one column / crystallisation cycle, and 25% (of 98% purity) following a second column / crystallisation cycle. The expense of the starting material 1 and the difficulty of the chromatography (requiring much time and large volumes of solvents because of the insolubility of 3) does not make this a very viable large-scale synthesis to provide compound of the purity required.

We used this route to make 3 in 5g quantity. This took a great deal of effort, to give 3 in 25% overall yield, at ca. 97% purity (impurity profile; small amounts of several unknown products). The cost of starting material 1 (4 kg) to make 1 kg of AQ4N was approximately £5000 at catalogue prices. While the cost is perhaps acceptable, this route is not operationally suitable for large-scale synthesis.

An alternative synthesis of 3 has been reported from the 1,4-difluoro compound 4 (Scheme 2; *J. Med. Chem.* 1991, 34, 2373). We confirmed the reported results, obtaining a 78% yield of 3 (94% pure before recrystallisation, with no major impurities). This reaction is suitable for scale-up, and it seems likely that material of adequate purity could be obtained by recrystallisation. The analogous dichloro compound 5 gave only trace amounts of 3 (Scheme 2), and the protected dibenzyl ether 6 was no better, indicating that the use of 4 was mandatory in this route.

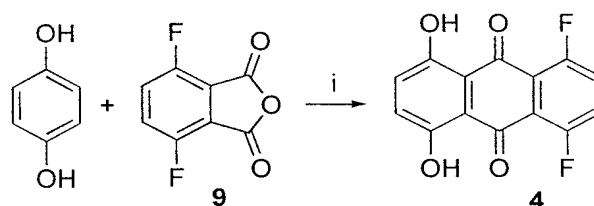


Synthesis of the key intermediate 4 was thus investigated. Successful halogen exchange has been reported (*Synth. Comm.* 1985, 15, 907) for the 1,4-dichloro-anthraquinone 7 ($7 \rightarrow 8$; Scheme 3), but this was not successful with the required analogues 5 or 6 (Scheme 3).



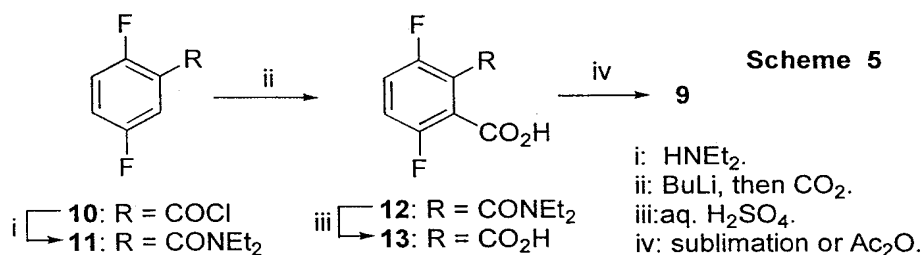
Scheme 3 i: KF/245 °C/25 h.

Another reported synthesis of **4** has been via the difluorophthalic anhydride **9** (*Synth. Comm.* 1995, 20, 2139), and we verified this synthesis, obtaining an 89% yield of pure **4** (Scheme 4).

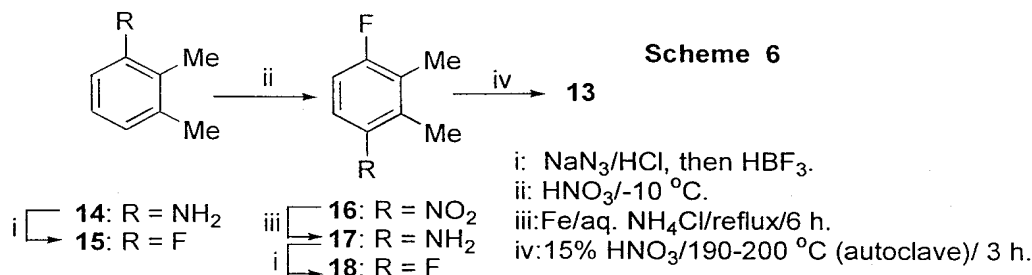
Scheme 4 i: AlCl₃/220 °C/1.5 h.

5

Operationally this is the best method, but the cost of starting material **9** (2 kg) is prohibitive (US\$ 230,000 at catalogue price, if available in this quantity). Syntheses of this also have to be considered. Two syntheses have been reported. In Scheme 5 (*Synth. Comm.* 1990, 20, 2139), the overall yield of **9** is 40% from the acid chloride **10** (US\$ 24/5g: Aldrich Chemical Co.). The overall yield is good, but the cost of **10**



(while much less than **9**) is still high, and the 4-step synthesis will add to costs, especially the BuLi step. Cost of starting material **10** (5 kg) is prohibitive (US\$ 24,000 at catalogue price, if available in this quantity).

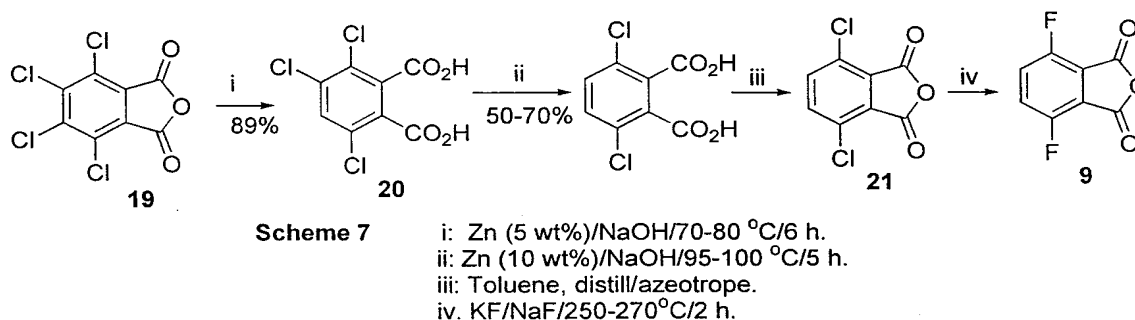


Scheme 6 outlines a synthesis from cheap 2,3-dimethylaniline **14** (US\$ 53/500g; Aldrich Chemical Co.). Fluorination followed by nitration gave **16** (J. Chem. Soc. 1963, 5554). This was converted to **17** and then by a second fluorination to **18**, followed by oxidation with nitric acid to the previously-mentioned **13** (see Scheme 5).

The lower cost starting material for Scheme 6 would probably be offset by the much lower overall yield reported (8%). This is largely due to a low yield (30%) in the $\text{17} \rightarrow \text{18}$ conversion.

10

A study of diverse reports (*Syn. Lett.* 1990, 339; *J. Org. Chem.* 1993, 58, 261; *Het. Chem.* 1995, 32, 907) suggests an alternative synthesis (Scheme 7).



The tetrachlorophthalic anhydride (**19**) is cheap (US\$ 63/3000g; Aldrich Chemical Co.), and can be dechlorinated in two successive reactions to give the dichlorophthalic anhydride **21** in 45–60% overall yield. The well-defined conditions listed are required to achieve clean product in each case. A single step from $\text{19} \rightarrow \text{21}$ does not work well, due to the differing requirements for the separate dechlorinations. The products (**19**, **20**, **21**) are not distinguishable by TLC, requiring NMR to determine purities. While **21** is also commercially available it is expensive (US\$ 59/1g; Aldrich Chemical Co.), and

it is probably cheaper to make it by the above method. The dichloro compound **21** has been reportedly converted into the desired difluoro analogue **9** in ca. 60% yield using KF (Bergmann *et al.*; *J. Chem. Soc.* 1964, 1194), but few details were given. However, it is difficult to repeat the reaction using the sketchy reported conditions, owing to
5 sublimation of the anhydride **21** at 250 °C. Alternative methods using solvents give only very low yields. This problem would have to be solved for this route to be viable.

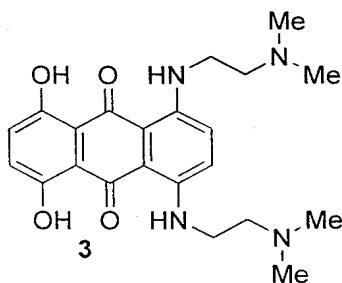
Synth. Comm., 1990, 20, 2139 uses the difluorophthalic anhydride **9** but does not mention the Bergmann *et al.* paper (*J. Chem. Soc.* 1964, 1194). Instead, it notes
10 “development of a practical synthesis of [3,6-difluorophthalic anhydride]”. This implies that the previous Bergmann *et al.* method is not practical. They then develop a quite different (but longer) route to this compound (Scheme 5, above).

The same authors, in an earlier paper (*Synth Comm* 1985, 15, 907), do specifically
15 reference the Bergmann *et al.* paper. They then go on to develop two alternative routes to the next compound in the synthesis (compound **4**, above), bypassing the need to make 3,6-difluorophthalic anhydride. This again implies that the Bergmann *et al.* method to make this compound is not practical.

20 We have now solved this problem by using a nitrogen atmosphere and repeated remelting of the sublimate to obtain useful results.

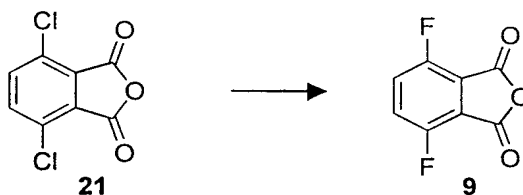
Thus the present invention provides a process for the preparation of the compound AQ4 of formula 3:

25



30

or a salt or *N*-oxide thereof, including the step:



5

Preferably the reaction is carried out using a nitrogen atmosphere.

Any method of mixing the reaction to ensure even heating and maximum contact between the melt of **21** and the inorganic fluoride may be used. However, preferably the reaction mixture is heated to cause sublimation of solid, with frequent remelting of the sublimate back into the reaction mixture. Gentle stirring internally aids reaction.

The reaction is preferably conducted over a layer of powdered anhydrous KF and/or NaF, and more preferably a mixture of anhydrous KF and NaF. Preferably the mixture of KF and NaF contains from 10% to 60% by weight of NaF and from 90% to 40% by weight of KF, and more preferably around 17% by weight of NaF and around 83% by weight of KF.

Preferably the reaction mixture includes:

20

5 parts by weight dichlorophthalic anhydride (**21**);
 10 to 25, especially around 20, parts by weight KF; and
 2 to 6, especially around 4 parts by weight NaF.

25 The reaction is preferably conducted at a temperature of 260–270 °C.

The above reaction step is a critical step and very dependent on conditions that were not reported by Bergmann *et al.*; *J. Chem. Soc.* 1964, 1194). Thus on a small scale (10 g), a bath temperature of 245–250 °C works better than 260–270 °C, giving a cleaner product and a higher yield. However, on a 100 g scale this temperature range did not work well, with the reaction only going part way. Because the reaction is heterogeneous (the compound **21** melts but the KF does not), efficient heat transfer is

30

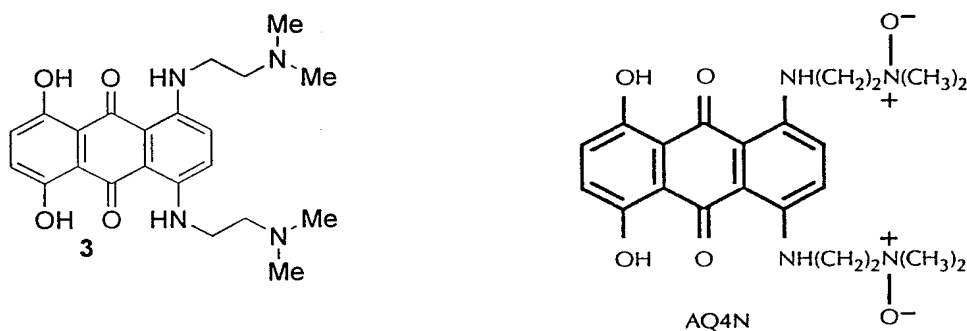
critical, and the margin between incomplete reaction (less than 260 °C) and rapid decomposition (greater than 270 °C) is very narrow. Something as simple as using a thick-walled flask greatly lowers yield.

- 5 We have found that using a thin-walled flask, and a mixture of KF (400 g) and NaF (80 g) for 100 g of **21** improves yields. This results in a looser reaction "cake" after the reaction is complete, allowing a more rapid removal of product by sublimation (at 140 °C to 170 °C, 0.3 mm Hg). In turn this results in less decomposition during sublimation, and a purer product.

10

Reagent ratio is also critical; if only half the amount of KF / NaF is used, there is essentially no reaction.

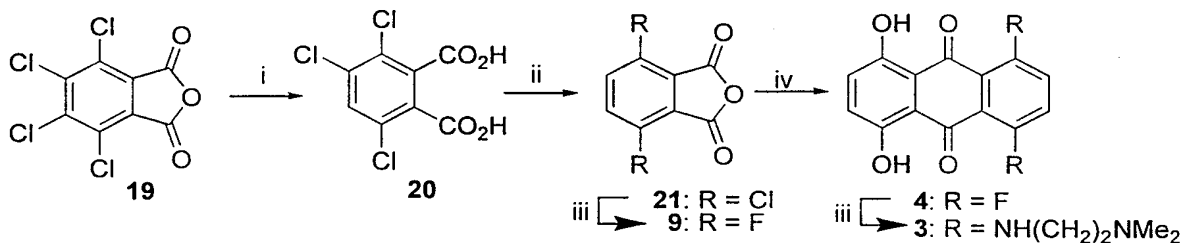
The reaction may be used to prepare AQ4 (**3**) or its *N*-oxide AQ4N:



15

Making the intermediate **9** via Scheme 7 this way is operationally acceptable (a three-step synthesis in about 35% overall yield). Cost of starting material **19** (4 kg) is trivial (US\$ 100 at catalogue price). We believe that the best (perhaps the only economically feasible) route to AQ4N is as follows (Scheme 8). This five-step synthesis from a cheap (US \$63/3 kg: Aldrich Chemical Co.) and readily-available starting material requires only one straightforward filtration chromatography step (at the end, to remove a few percent of the monochloro compound **23**, arising from the analogous monochloro anhydride **22**).

20



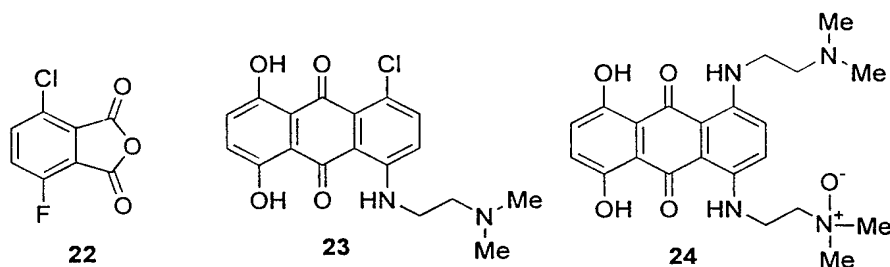
Scheme 8

i: Zn (5 wt%)/NaOH/70-80 °C/6 h. ii: Zn (10 wt%)/NaOH/95-100 °C/5 h.
 iii: KF/NaF/260-270 °C/2-3 h. iv: Hydroquinone/AlCl₃/200±5 °C/2 h.
 v: N,N-dimethylethylenediamine/20 °C/45 h.

This delivers AQ4 in overall 15% yield (22% on a gram/gram basis) in ≥97% purity directly off the column (containing one major unknown impurity of ca. 1%). All steps have been carried out on at least a 100 g scale, and are potentially scaleable further.

Oxidation of the AQ4 product using, for example, Davis reagent, gives the bis-*N*-oxide AQ4N. The route may be modified to make the mono-*N*-oxide 24, by limiting the degree of oxidation that occurs.

10



Synthetic Details

3,4,6-Trichlorophthalic Acid (20). This compound was prepared by modifications to the literature method of *Syn. Lett.*, 1990, 339. A mixture of 3,4,5,6-tetrachlorophthalic anhydride (19) (Aldrich Chemical Co., 100 g, 0.35 mmol) and NaOH (50.0 g, 1.25 mmol) in water (1000 mL) was stirred at 50–60 °C (bath) for 45 min under a nitrogen atmosphere. Zinc dust (70.0 g, 1.07 mmol) was then added portionwise over 10 min, and the mixture was stirred at 70–80 °C for a further 6 h. The reaction was cooled to

room temperature and filtered through a bed of Celite, and the filter and residue was washed successively with 0.1N NaOH (2 x 100 mL) and H₂O (2 x 100 mL). The combined filtrate was acidified with conc. HCl to pH \leq 1, and the colourless precipitate was collected by filtration and washed with 0.1N HCl (3 x 100 mL). The damp solid
5 was stirred with EtOAc (600 mL) and acidified with conc. HCl until all the solids had dissolved. The EtOAc layer was separated and the aqueous portion further extracted with the same solvent (2 x 100 mL). The combined EtOAc solution was dried (Na₂SO₄), filtered, and evaporated under reduced pressure give 3,4,6-trichlorophthalic acid (**20**) (83.5 g, 89%) as a colourless solid; m.p. (without recrystallisation) 151–153
10 °C (lit. m.p. 150–153 °C). ¹H NMR identical to literature.

3,6-Dichlorophthalic Anhydride (**21**). This compound was prepared by modifications to the literature method of *J. Het. Chem.*, 1995, **32**, 907. Zinc dust (165 g, 2.52 mmol) was added portionwise (over 15 min) to a homogenous mixture of **20** (118 g, 0.437
15 mmol) and NaOH (120 g) in water (1200 mL) stirred at 90 °C (bath) under a nitrogen atmosphere. The resulting heterogeneous mixture was further stirred at 95–100 °C for 5 h, then cooled to room temperature and filtered through a bed of Celite. The filter and residue was washed with water (3 x 100 mL), and the combined filtrate was acidified with conc. HCl (250 mL) and extracted with EtOAc (2 x 300 mL). The
20 combined EtOAc solution was dried (Na₂SO₄), filtered and evaporated under reduced pressure to give crude 3,6-dichlorophthalic acid (100 g). Toluene (1000 mL) was added to this solid, and the mixture was distilled until the distillate was clear (after about 600 mL had been collected). The hot concentrate was gravity-filtered, and the residue was washed with hot toluene (3 x 50 mL). The combined filtrate was seeded
25 and chilled to give 3,6-dichlorophthalic anhydride (**21**) as a colourless solid (67.0 g, 72%); m.p. 187–190 °C (lit. m.p. 188–191 °C). ¹H NMR identical to literature.

3,6-Difluorophthalic Anhydride (**9**). This compound was prepared as reported previously without conditions in the literature (Bergmann *et al.*; *J. Chem. Soc.*, 1964,
30 1194), and well-defined conditions and operating procedures were developed. In a 1 L round-bottomed thin-wall flask was placed a layer of **21** (100 g, 0.467 mol), over a layer of powdered mixed anhydrous KF (400g) / NaF (80 g). This packing was not

disturbed, but dried in a vacuum oven at 140 °C to 170 °C at 20 mm Hg for 7 h. The flask was transferred to an oil bath such that the oil level was about 1 cm above the solid layer. The flask was evacuated again by a water pump, and then filled with nitrogen gas. The bath was then heated to 260–270 °C and held at this temperature.

5 After about 20 min, a considerable amount of solid sublimed onto the top of the reaction flask, and the flask was lowered gently into the oil bath until the oil level reached to the neck of the flask. When all the sublimed solid melted and flowed back onto the solid layer, the flask was returned to its original level in the oil bath. This operation was repeated at about 20 min intervals, until a light brown layer of KF / NaF

10 was observed after 2–3 h. The reaction mixture was then sublimed at 140 °C to 170 °C (3 mm Hg) in a Kugelrohr apparatus, giving a solid product that contained mainly 3,6-difluorophthalic anhydride (**9**) (ca. 90% by NMR) (64.8 g, 76%); m.p. (toluene) 211–214 °C (lit. m.p. 212 °C [Bergmann *et al.*; *J. Chem. Soc.*, 1964, 1194]; 206–207 °C [*J. Chem. Soc.*, 1963, 3475]). ¹H NMR identical with authentic sample (Aldrich

15 Chemical Co.).

The only significant impurity (ca. 5–10%) present in the sublimed product is considered to be the intermediate 3-chloro-6-fluorophthalic anhydride (**22**). However, the above material was used for the next step without further purification.

20 1,4-Difluoro-5,8-dihydroxyanthracene-9,10-dione (**4**). This compound was prepared by modifications to the literature method of *Synth. Comm.*, 1990, **20**, 2139. A mixture of the sublimed product (**9**) from the above reaction (100 g, 0.55 moles), hydroquinone (63.7 g, 0.58 moles), NaCl (127 g, 2.22 moles) and powdered anhydrous AlCl₃ (833 g,

25 6.26 moles) was placed in a 5 L flask equipped with a condenser. The reactants were well-mixed by shaking, then heated over 1–2 hours to 200±5 °C (bath) under a nitrogen atmosphere (there was very large gas evolution during the heating process). After a further 2 hours at 200±5 °C, the melt was poured onto ice and conc. HCl (1.6 L) was added. The mixture was stirred at room temperature overnight, and the reddish

30 brown precipitate was collected, washed with H₂O and dried to give crude 1,4-difluoro-5,8-dihydroxyanthracene-9,10-dione (**4**) (151 g, 98%), m.p. 301–304 °C (lit. m.p. 318–319 °C). This crude product was virtually insoluble in all solvents, and

showed (by TLC in EtOAc / petroleum ether 1:3) only one minor impurity (probably 1-chloro-4-fluoro-5,8-dihydroxyanthracene-9,10-dione). ¹H NMR agreed well with literature. This material was used for the next step without further purification.

- 5 1,4-Bis[[2-(dimethylamino)ethyl]amino]-5,8-dihydroxyanthracene-9,10-dione (3: AQ4). This was prepared by modifications to the literature method of *J. Med. Chem.*, 1991, **34**, 373). A mixture of crude **4** (29.6 g, 107 mmol) and *N,N*-dimethylethylenediamine (99.5 mL, 908 mmol) in pyridine (400 mL) was stirred at room temperature under nitrogen atmosphere for 45 h. The mixture was then poured into
10 brine (1600 mL) and stirred at room temperature for 30 min. The blue precipitate was collected by filtration, washed with 1 N NH₄OH (1000 mL), and dried under vacuum over KOH / silica for 15 h. This crude product (21.5 g) was dissolved in CH₂Cl₂ and transferred to a silica gel flash column. The faster-running pink impurity was eluted in a gradient of MeOH (0.5, 1 and 2%) in CH₂Cl₂, and was tentatively assigned as
15 1-[[2-(dimethylamino)ethyl]amino]-4-chloroanthracene-9,10-dione (**3**: one R = Cl) (1.6g, 4%): m.p. CH₂Cl₂) 165–167 °C; ¹H NMR (CDCl₃) δ 12.97 (s, 1 H, exchangeable with D₂O, OH), 12.92 (s, 1 H, exchangeable with D₂O, OH), 10.04 (s, 1 H, exchangeable with D₂O, NH), 7.50 (d, *J* = 9.5 Hz, 1 H, H-3), 7.24 (d, *J* = 9.2 Hz, 1 H, H-6), 7.20 (d, *J* = 9.2 Hz, 1 H, H-7), 6.98 (d, *J* = 9.5 Hz, 1 H, H-2), 3.40 (q, *J* = 6.3
20 Hz, collapse to t after D₂O, 2 H, NHCH₂), 2.67 (t, *J* = 6.3 Hz, 2 H, NHCH₂CH₂), 2.35 (s, 6 H, NCH₃). Anal. (C₁₈H₁₇ClN₂O₄·½H₂O) C, H, N.

The blue band was excised from the column and extracted successively with CH₂Cl₂ / MeOH (10:1) and CH₂Cl₂ / MeOH / Et₃N (90:10:1). The combined extracts were
25 filtered and evaporated to give 1,4-bis[[2-(dimethylamino)ethyl]amino]-5,8-dihydroxyanthracene-9,10-dione (AQ4; **3**) (17.9 g, 41%): m.p. 240–242 °C (without recrystallisation) (lit. m.p. 236–238 °C). ¹H NMR identical with the authentic sample. When the above reaction was repeated using 100 g of **4** for 48 h, the yield of **3** was 36%.

30

1,4-Bis[[2-(dimethylamino)ethyl]amino]-5,8-dihydroxyanthracene-9,10-dione bis-*N*-oxide (AQ4N). A stirred solution of **3** (17.75 g, 43.1 mmol) in CH₂Cl₂ / MeOH

(5:1) (600 mL) was treated dropwise over 30 min with a solution of 2-benzene-sulfonyl-3-phenyloxaziridine (Davis reagent: *J. Org. Chem.* 1982, 47, 1775) (25.7 g, 98.2 mmol) in CH₂Cl₂ (200 mL). After addition, the mixture was stirred at 20 °C in the dark for a further 90 min. It was then concentrated under reduced pressure at 24–26 °C (bath temperature) to ca. 100–200 mL, and then diluted successively with EtOAc (400 mL) and petroleum ether (400 mL). The homogeneous mixture was stirred at 20 °C for 15 min, then kept at -10 °C for 2 h. The blue precipitate was collected by filtration, washed with EtOAc / petroleum ether (1:1; 4 x 100 mL), and suctioned dry. It was then dissolved in MeOH (200 mL) and the solution was treated with anhydrous HCl gas until it remained acidic (pH ca. 2). After storing at -10 °C overnight, the precipitate was collected by filtration and washed successively with MeOH / EtOAc (1:1; 5 x 30 mL) and EtOAc (2 x 30 mL), and dried under vacuum to give AQ4N dihydrochloride (17.7 g, 80%), m.p. 243–245 °C. HPLC shows a purity of ca. 98.5%, with ca. 0.5% of the mono-*N*-oxide **24** (a decomposition product) and ca. 1% of an unknown impurity.

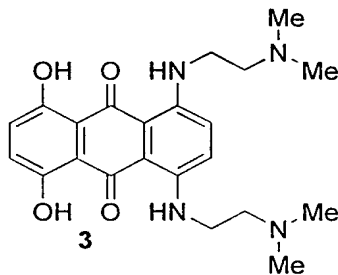
Notes

1. AQ4N was found to be somewhat unstable in MeOH solution at 20 °C in daylight, decomposing slowly to numerous other products.

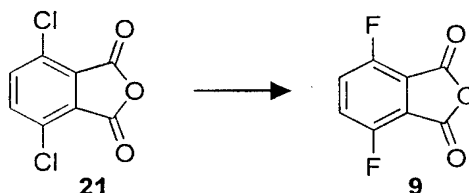
2. The solid dihydrochloride should be stored in a sealed container in a cold dark place (preferably a freezer). Before opening such containers they should be allowed to warm to room temperature, since the dihydrochloride (and AQ4N) absorb moisture particularly rapidly when cold.

Claims

1. A process for the preparation of the compound AQ4 of formula 3:



or a salt or *N*-oxide thereof, including the step:



2. A process as claimed in claim 1 in which the reaction is carried out using a nitrogen atmosphere.
3. A process as claimed in claim 1 or 2 in which the reaction mixture is heated to cause sublimation of solid, with frequent remelting of the sublimate back into the reaction mixture.
4. A process as claimed in any preceding claim in which the reaction is conducted over a layer of powdered anhydrous KF and/or NaF.
5. A process as claimed in claim 4 in which the reaction is conducted over a mixture of anhydrous KF and NaF.
6. A process as claimed in claim 5 in which the mixture of KF and NaF contains from 10% to 60% by weight of NaF and from 90% to 40% by weight of KF.

7. A process as claimed in claim 6 in which the mixture of KF and NaF contains around 17% by weight of NaF and around 83% by weight of KF.

8. A process as claimed in claim 5 in which the reaction mixture includes:

5

5	parts by weight	dichlorophthalic anhydride (21);
10 to 25	parts by weight	KF; and
2 to 6	parts by weight	NaF.

10 9. A process as claimed in claim 5 in which the reaction mixture includes:

5	parts by weight	dichlorophthalic anhydride (21);
around 20	parts by weight	KF; and
around 4	parts by weight	NaF.

15

10. A process as claimed in any preceding claim in which the reaction is conducted at a temperature of 260–270 °C.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02337

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C221/00 C07C225/36 C07C291/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 004 293 A (AMERICAN CYANAMID CO) 28 March 1979 (1979-03-28) page 9 -page 24 ---	1
A	WO 91 05824 A (NAT RES DEV) 2 May 1991 (1991-05-02) example 6 ---	1
A	E.D. BERGMANN ET AL. : "Preparation of 3,6,-difluorophthalic anhydride" JOURNAL OF THE CHEMICAL SOCIETY, 1964, pages 1194-1195, XP002123300 LETCHWORTH GB cited in the application page 1195, last paragraph --- -/--	1



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

29 November 1999

Date of mailing of the international search report

15/12/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Pauwels, G

INTERNATIONAL SEARCH REPORT

Inter: nal Application No

PCT/GB 99/02337

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>KRAPCHO, A. PAUL ET AL: "The synthesis of 1,4-difluoro-5,8-dihydroxyanthracene-9,10-dione and ipso substitutions of the fluorides by diamines leading to 1,4-bis'(aminoalkyl)amino!-5,8-dihydroxyanthracene-9,10-diones"</p> <p>SYNTH. COMMUN. (1990), 20(14), 2139-46 , XP000856535</p> <p>the whole document</p> <p>-----</p>	1

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 99/02337

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2004293 A	28-03-1979	US 4138415 A	06-02-1979
		AR 225884 A	14-05-1982
		AT 359484 B	10-11-1980
		AT 590678 A	15-04-1980
		AU 3877678 A	14-02-1980
		BE 869688 A	12-02-1979
		CA 1140923 A	08-02-1983
		CH 644840 A	31-08-1984
		DD 139256 A	19-12-1979
		DE 2835661 A	01-03-1979
		DK 358678 A,B,	16-02-1979
		ES 472508 A	16-10-1979
		ES 479234 A	16-07-1979
		FI 782481 A,B,	16-02-1979
		FR 2400504 A	16-03-1979
		GR 74415 A	28-06-1984
		IE 47253 B	08-02-1984
		IL 55218 A	31-03-1983
		IT 1107773 B	25-11-1985
		JP 1052365 B	08-11-1989
		JP 1581792 C	11-10-1990
		JP 54063064 A	21-05-1979
		JP 1063556 A	09-03-1989
		JP 1593641 C	14-12-1990
		JP 2017534 B	20-04-1990
		KR 8400053 B	31-01-1984
		KR 8400793 B	12-06-1984
		NL 7808475 A,C	19-02-1979
		NO 782756 A,B	16-02-1979
		NO 820290 A,B	16-02-1979
		NZ 187989 A	13-07-1981
		PH 19232 A	12-02-1986
		PT 68420 A	01-09-1978
		SE 445996 B	04-08-1986
		SE 7807987 A	16-02-1979
		US 4888137 A	19-12-1989
		US 4540519 A	10-09-1985
		US 4820738 A	11-04-1989
		US 4197249 A	08-04-1980
		ZA 7804197 A	25-07-1979
		ES 479233 A	16-07-1979
		CA 1099213 A	14-04-1981
		PH 16830 A	06-03-1984
		US 4418078 A	29-11-1983
		CA 1116522 A	19-01-1982
		PH 20730 A	02-04-1987
		US 4540583 A	10-09-1985
		CA 1099710 A	21-04-1981
		PH 16104 A	30-06-1983
WO 9105824 A	02-05-1991	AT 101181 T	15-02-1994
		AU 634125 B	11-02-1993
		AU 6539590 A	16-05-1991
		CA 2038934 A	14-04-1991
		DE 69006482 D	17-03-1994
		DE 69006482 T	11-05-1994
		DK 450021 T	07-03-1994
		EP 0450021 A	09-10-1991

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter: nal Application No

PCT/GB 99/02337

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9105824 A		ES 2062558 T	16-12-1994
		GB 2237283 A,B	01-05-1991
		JP 2854971 B	10-02-1999
		JP 4502166 T	16-04-1992
		NZ 235658 A	23-12-1992
		PT 95584 A,B	13-09-1991
		US 5132327 A	21-07-1992
<hr/>			